REMARKS

Claims 7-10, 13-16, 19, 20, 27-29, 31-33, and 35-42 were pending prior to this response, and of these, claims 13-16, 28, 32, 35, and 36 are withdrawn from consideration. Claims 7-10, 19, 20, 27, 29, 31, 33, and 37-42 stand rejected. In this response, claims 13-16, 28, 32, 35, and 36 have been canceled. Claims 7-10, 19, 20, 27, 29, 31, 33, and 37-42 are therefore pending.

Rejections Under 35 USC § 103

Applicant notes that the rejection of claims 7-9, 19, 20, 27, 29, 31 and 33 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Adair *et al.* in view of *King et al.* (U.S. Pat. No. 6,307,026 B1) and Hodits *et al.* (Journal of Biological Chemistry, 1995), has been withdrawn. Applicant acknowledges that the claims have been determined to be patentable over these references, and accordingly, no further discussion is required.

Claims 7-9, 19, 20, 27, 29, 31, 33 and 37-42 were previously rejected in the April 11, 2005 Office Action under 35 U.S.C. 103(a) as allegedly being unpatentable over Adair *et al.*, Kipriyanov *et al.*, Pack *et al.*, and Hodits *et al.*

Claims 7-9, 19, 20, 27, 29, 31, 33 and 37-42 are directed to multivalent recombinant antibody against ICAM-1 having an apparent affinity constant for ICAM-1 of no less than 10^9 M^{-1}, wherein said antibody comprises three or more antigen binding domains for ICAM-1, and wherein said antibody is polymerized through a coiled-coil sequence.

Adair *et al.*, which is entitled "Humanized CDR-Grafted Anti-ICAM-1 Antibodies, Methods of Preparation and Usage Thereof", does not relate to multivalent antibodies. The Examiner acknowledges that Adair *et al.* does not teach a multivalent recombinant antibody having more than two antigen binding sites (May 21, 2004 Office Action, page 3, page 3, May 21, 2005 Office Action). Thus it is not surprising that Adair *et al.* fails to suggest an antibody directed to ICAM-1 having three or more antigen binding domains for ICAM-1.

Interestingly, Adair *et al.* recites numerous recombinant antibody molecules (RAM) and CDR-grafted humanized antibody molecules (HAM) that could be used, but makes no mention or suggestion of a bispecific or multivalent antibody. See page 27, lines 24-32 of published WO91/16927, which describes:

> The RAMs or HAMs of the present invention may comprise: a complete antibody molecule, having full length heavy and light chains; a fragment thereof, such as the Fab or (Fab')2 fragment; a light chain or heavy chain monomer or dimer, or a single chain antibody, e.g., a single chain FV in which heavy and light chain variable regions are joined by a peptide linker; or any other recombinant or CDR-grafted molecule with the same specificity as the original donor antibody. Similarly the CDR grafted heavy and light chain variable region may be combined with other antibody domains as appropriate.

Also, the fact that Adair *et al.* makes explicit reference to numerous antibody variants without any mention of a multivalent antibody is evidence that they failed to contemplate an antibody directed to ICAM-1 that would have a higher specificity that an original donor antibody. This is substantiated by the explicit reference "with the same specificity as the original donor antibody" in Adair *et al.* , which appears to be in opposite to the assertion by the Examiner that increasing valency of an antibody goes hand in hand with increasing the affinity of an antibody. See page 5 of the April 11, 2005 office action, which states:

> It would have been obvious to one of skill in the art at the time the invention was made to increase the affinity of an antibody complex by increasing the valency of the complex as taught by Kipriyanov et al.

The Examiner has acknowledged that the antibodies in Adair *et al.* were said to have the same specificity as the R6-5-D5 antibody, and cites page 31, lines 19-25 of Adair *et al.* in support of this position (see May 21, 2004 Office Action, page 3). Applicant notes that the Examiner has not refuted the evidence provided by Applicant that binding affinities for R6-5-D5 antibodies were reported by Casasnovas *et al.* as clearly being less than 10^9 M^{-1} (See Response dated November 22, 2004, and Casasnovas *et al.*, *J. Biol. Chem.* 270:13216 (1995) and Casasnovas *et al.*, *J. Virol.* 72:6244 (1998) provided as Exhibits).

Instead, the Examiner responded by characterizing the data regarding reported binding affinities for the notes antibodies as merely argument and asserting that an apparent affinity of 10^9 M^{-1} falls within the realm of optimizing the composition (April 11, 2005 Office Action, pages 3-4). Interestingly, the Examiner invites further evidence but has failed to consider, comment, or rebut the evidence presented in Applicant's last response (see April 11, 2005 Office Action, page 4, stating "Barring any evidence to the contrary the presumption is that the prior art antibodies will bind ICAM-1 epitopes with the required specificity.").

The Office Action asserts that Kipriyanov *et al.* teaches the production of an antibody complex that uses single chain antibody fragments that are linked to streptavidin. The Examiner

acknowledges that Kipriyanov *et al.* fails to teach an anti ICAM-1 multivalent complex. Kipriyanov *et al.* reports that a scFv:: strep tetramer has a 35 times higher apparent affinity than a scFv monomeric single chain antibody (Abstract). However, the apparent affinity reported for this tetramer in Kipriyanov *et al.* was 15.6 X 10^{-7}M (see Table II). Thus, Kipriyanov *et al.* reports an apparent affinity that is an order of magnitude less than the affinity specified in claim 1 of the instant invention. This could be due to the fact that the multimeric antibodies in Kipriyanov *et al.* are linked together by streptavidin, which is a totally different chemical structure than a coiled-coil sequence (claim 1). In fact, Kipriyanov *et al.* says nothing about an antibody that is polymerized through a coiled-coil sequence.

It is also important to note that the streptavidin used in Kipriyanov *et al.* is highly immunogenic, such that it would render the multimeric antibodies useless for therapeutic purposed in animals. Accordingly, one of skill in the art would not be motivated to modify the antibodies of Adair *et al.* to in an attempt to increase their affinity with the streptavidin linkers of Kipriyanov *et al.* Thus, Kipriyanov *et al.* is not properly combinable with Adair *et al.* Even is such a combination was made, the resultant antibody would have a binding affinity that is an order of magnitude less that the antibodies specified in claim 1 and the antibodies would be highly immunogenic and thus not useful for treatment in a host (see claims 27-29, 31, 33, etc.).

According to the Office Action, Pack *et al.* is said to teach a multivalent trimeric or tetrameric single chain antibody construct obtained by the addition of the leucine zipper dimerization domain of GCN4. The Office Action acknowledges that Pack *et al.* does not teach an anti ICAM-1 multivalent complex. Further, Pack *et al.* provides no teaching or suggestion to make an antibody according to claim 1 ("A multivalent recombinant antibody against ICAM-1, wherein said antibody has an apparent affinity constant for ICAM-1 of no less than 10^9 M^{-1}, wherein said antibody comprises three or more antigen binding domains for ICAM-1, and wherein said antibody is polymerized through a coiled-coil sequence" (emphasis added)).

Hodits *et al.* reports antibodies against the low density lipoprotein receptor (LDL) inhibit rhinovirus infection (Abstract). Hodits *et al.* further reports that "The protection is even stronger in the presence of the anti-*myc*-antibody 9E10 which renders the scFv7 bivalent by binding two molecules via the *myc*-sequence tag which is COOH terminally fused to the antibody fragment." The asserted bivalent molecules are totally different than those of the instant invention. They recognize a completely different antigen, and they are allegedly made bivalent by a separate

antibody that recognized tag sequences. One of skill in the art would not expect such a bivalent construct to be analogous or predictive of the instant invention. Moreover, one of skill in the art, having read Hodits *et al.*, would not be lead to take a completely different approach for producing a multivalent antibody such as that specified in the claims, let alone have a reasonable expectation of success that such a molecule would have an enhanced affinity. Also, as Applicant has noted in the response dated November 22, 2004, Hodits *et al.* fails to provide any data which substantiates the conclusion that the antibodies were indeed bivalent. Notwithstanding the deficiencies of Adair *et al.*, Kipriyanov *et al.* and Pack *et al.*, Hodits *et al.* does not complete a *prima facie* case required for a rejection under 35 U.S.C. §103.

Regarding the rejection of claims 19, 27, 29, 31, 33, and 37-42, the only rationale provided by the Examiner is the following:

> Formulating a combination of ICAM-1 directed antibodies and LDL antibodies to a single use formulation would have been motivated by Hodits et al. which indicates that rhinoviruses gain entry into the host cell via the LDL receptor (minor group) and via the ICAM-1 (major group). A formulation containing antibodies directed to both group would provide protection against rhinovirus displaying surface molecules associated different serotypes (see Hodits et al. page 24084, column 2, 2nd paragraph).

However, Hodits *et al.* it self fails to teach or suggest a formulation or a method for treating a rhinovirus infection comprising two multivalent antibodies, where one is directed to ICAM-1 and another is directed to the LDL receptor. None of the references cited by the Examiner teach or suggest a method of preventing acute otitis media in a host comprising administering to the nasal epithelium of the host a pharmaceutically effective amount of a first multivalent recombinant antibody and a second multivalent recombinant antibody, where the first antibody has an apparent affinity constant for ICAM-1 of no less than 10^9 M^{-1} and is polymerized through a coiled-coil sequence, and where the second antibody has an apparent affinity constant for LDL receptor of no less than 10^8 M^{-1} (claim 33); or a multivalent recombinant antibody that has an apparent affinity constant for ICAM-1 of no less than 10^{10} M^{-1} (claims 37-42).

The references cited by the Examiner also fail to teach or suggest a topical formulation for preventing rhinovirus infection comprising a multivalent recombinant antibody against ICAM-1 having an apparent affinity constant for ICAM-1 of no less than 10^9 M^{-1} (claim 19); a

method of preventing the common cold comprising administering to the nasal epithelium of a host a pharmaceutically effective amount of a multivalent recombinant antibody having an apparent affinity constant for ICAM-1 of no less than 10^9 M^{-1} (claim 27); a method of preventing the common cold in a host comprising the step of administering to the nasal epithelium of said host a pharmaceutically effective amount of a first multivalent recombinant antibody and a second multivalent recombinant antibody, where first antibody has an apparent affinity constant for ICAM-1 of no less than 10^9 M^{-1} and is polymerized through a coiled-coil sequence, and where the second antibody has an apparent affinity constant for LDL receptor of no less than 10^8 M^{-1} (claim 29); or a method of preventing acute otitis media in a host, comprising administering to the nasal epithelium of the host a pharmaceutically effective amount of a multivalent recombinant antibody that has an apparent affinity constant for ICAM-1 of no less than 10^9 M^{-1} (claim 31). Applicant respectfully submits that the Examiner has failed to provide a rationale for the rejection of these claims, and accordingly has failed to establish a *prima facie* case as required under 35 U.S.C. § 103(a).

The combination of Adair *et al.*, Kipriyanov *et al.*, Pack *et al.*, and Hodits *et al.* does not provide a suggestion to modify an antibody to ICAM-1 reported in Adair *et al.* to make it multivalent through a coiled-coil sequence such that it has an apparent affinity constant for ICAM-1 of no less than 10^9 M^{-1}. The cited art has also failed to indicate that this approach, if tried, would likely succeed. Consequently, it appears that the Examiner is looking at Applicants' invention in hindsight to modify the cited art to produce the instant invention.

It is the law that the art that may be relied on by the Patent Office constitutes only those items that one of ordinary skill in the art would have selected without the advantage of hindsight or knowledge of the invention. *Union Carbide Corporation v. American Can Company*, 724 F.2d 1567, 220 USPQ 584, 591 n.6 (Fed. Cir. 1984); *In re Antle*, 444 F.2d 1168, 170 USPQ 285 (CCPA 1971). The Federal Circuit has repeatedly cautioned against employing hindsight by using applicants' disclosure as a blueprint to reconstruct the claimed invention out of isolated teachings of the alleged prior art. *E.g., Grain Processing Corp. v. American Maize-Products Co.*, 840 F.2d 902, 907, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time.");

W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (The problem with combining references using hindsight to render a claimed invention obvious is that it "simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability."). Applicant respectfully submits that the Examiner has failed to avoid such improper hindsight reconstruction in the instant rejections.

It is well established that "To establish a *prima facie* case, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference or references, when combined, must teach or suggest all the claim limitations. MPEP 706.02(j), citing, *In re Vaeck*, 947 F.2d 488, 20 USPQ 2d 1438 (Fed. Cir. 1991) (emphasis added).

Applying the law to the current facts, Applicants respectfully submit that the Examiner has failed to complete a *prima facie* case as required under 35 U.S.C. §103 because it has failed to establish appropriate suggestion or motivation, a reasonable expectation of success, and that a combination of the references teach or suggest all the claim limitations. Accordingly, Applicant request that the rejections under 35 U.S.C. §103 be reconsidered and withdrawn.

CONCLUSION

For the reasons set forth above, Applicant respectfully submits that all pending claims in the application are in condition for allowance. The Examiner is encouraged to contact the undersigned if it is believed this would expedite prosecution. For the reasons described and supported above, Applicants respectfully submit that all pending claims are now in condition for allowance. That said, should any issues or questions remain, the Examiner is encouraged to telephone the undersigned at (619) 744-2240 so that they may be promptly resolved.

In the unlikely event the transmittal letter is separated from this document and the Office determines that an extension and/or other relief is required, Applicants petition for any required relief, including extensions of time, and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to the credit card disclosed in form PTO-2038 filed with this document

Respectfully submitted,

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